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Title: How can we reduce the high prevalence of cigarette smoking among persons with serious mental illnesses?

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Summary

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High smoking rates in people with serious mental illness (SMI) contribute significantly to their disproportionately high morbidity and premature mortality. There is an urgent need to help people with SMI quit smoking. This paper: critically discusses competing explanations for the high rates of smoking in persons with SMI and the effectiveness of available smoking cessation interventions. It argues for trialing harm reduction options, such as NRT and e-cigarettes as long term substitutes for cigarettes in smokers with SMI who are unable to quit. Smoke free psychiatry units should provide smoking cessation support on admission and after discharge.

Introduction

Serious mental illnesses (SMI) include diagnosable mental, behavioural or emotional disorders which cause serious functional impairment, and substantially interfere with or limit one or more major life activities.[1]The prevalence of cigarette smoking in persons with SMI such as schizophrenia, schizoaffective disorders, bipolar disorder and, major depression, is much higher than in the general population.[2,3] The association of smoking is strongest and most consistent in persons with schizophrenia who are 3-7 times more likely to smoke compared to general population,[4,5] Those with bipolar disorder 3-4 times more likely[6] and those with major depression are twice as likely to smoke,[7] as people without these disorders. Tobacco smoking is a major contributor to the high premature mortality and severe morbidity in persons with SMI.[2] Heavy daily smoking in combination with limited access to quality health care and dyslipidaemia produced by some antipsychotic medication increases the risk of cancers and heart disease [8,9] and reduces life expectancy by 10-15 years compared to people without SMI.[10] SMI is also associated with dependence on alcohol and other substances which further compounds their risk of adverse health outcomes.[11–14]

What should be done to reduce smoking in persons with serious mental illnesses?[15] The answer depends on answers to the following questions: What factors drive the high prevalence of smoking in this population? How easy or difficult it is for persons with SMI to quit smoking? Are smoke free psychiatric facilities an appropriate policy response? Should we consider tobacco harm reduction (THR), i.e. encouraging heavy smokers with SMI to use non-smoked nicotine products instead of smoking tobacco?

Smoking in SMI: Cause or effect?

A number of theories attempt to explain the high smoking prevalence in people with SMI, especially schizophrenia and major depression. These hypotheses are based on one of the following premises - SMI causes smoking (self-medication hypothesis) [16,17], smoking causes SMI (causal hypothesis) and both smoking and SMI result from a common aetiology (shared vulnerability hypothesis).[18,19] A summary of evidence for and against each of these hypotheses are presented in Table 1.

These three hypotheses have different implications for policies to reduce cigarette smoking in persons with SMI. The self-medication and the shared vulnerability hypotheses may be seen as favouring more lenient policies towards cigarette smoking in these persons. This could include THR using alternative non-combustible nicotine products such as pharmaceutical nicotine products, smokeless tobacco and nicotine vaporisers, such as, e-cigarettes. The causal hypothesis on the other hand may be seen as justifying an intensification of efforts to discourage smoking in persons with SMI (e.g. hospital smoking bans) with the aim of encouraging abstinence from all forms of nicotine. Evidence for causality should be weighed individually for different mental illnesses when deciding upon these tobacco control policies.

Smoking cessation in people with mental illness

Smoking uptake is higher and cessation rates are lower in people with SMI than without SMI.[6,20] Persons with SMI are also often heavily dependent on nicotine[21] and experience more severe withdrawal symptoms when they stop smoking than people without SMI.[22] Co-existing alcohol and substance abuse may potentiate the reinforcing effects of nicotine, making quitting even more difficult for those with multiple dependence diagnoses.[13,23] Despite these barriers, people with SMI report that they are as motivated to stop smoking as people without SMI.[24] The low cessation rate among people with SMI has been attributed to a combination of a failure to promote smoking cessation in this population and the difficulty that they have in accessing smoking cessation services.[9,25,26]

Smokers with SMI, like all smokers, can improve their physical and mental health by quitting.[27] However, many of these smokers, and the mental health professionals who care for them, believe that their mental health will worsen if they quit smoking. For this reason staff may not encourage quit attempts.[25]This belief is inconsistent with the evidence that smoking cessation reduces depression, anxiety and stress, people with SMI.[27]

Smoking cessation guidelines for all smokers including those with SMI recommend pharmacotherapy in combination with behavioural interventions.[28,29] The most effective pharmacotherapies include nicotine replacement therapy (NRT), the atypical anti-depressant bupropion and varenicline, a nicotinic receptor partial agonist.[30] Behavioural interventions include brief advice, financial incentives for quitting, self-help material and counselling.[28,29,31]

The effectiveness of these smoking cessation pharmacotherapies has been demonstrated in numerous clinical trials in the general population[32–34] but it has not been extensively tested in

people with SMI.[35] Concerns about the side effects of varenicline and bupropion have promoted caution in the use of these drugs in this people with SMI. A network meta-analysis of 14 RCTs of smoking cessation pharmacotherapies in smokers with SMI found that bupropion and varenicline were both effective and acceptable (OR= 4·51 and 5·17 respectively).[30] However, the evidence base was rated as of very low in quality.[30] Some studies suggest that NRT may be effective in reducing smoking and maintaining abstinence in the long term in smokers with SMI.[36,37]

Behavioural support for smoking cessation in people with SMI is effective at long term follow up (RR 1·33, CI 0·96–1·8),[38] so too is ppharmacotherapy combined with counselling or motivational interviewing, or alone.[39–41] Mobile phone based support and internet assisted cessation is effective in general population, but have not been well studied in smokers with SMI.[42–44] It is unclear which smoking cessation options are best for people with SMI but the limited evidence suggests that those that work for smokers in the general population may also be effective for smokers with SMI with or without co-morbid substance abuse disorders.[40,45] Abstinence from tobacco may also reduce relapse to substance abuse in people with co-morbid mental illness.[45]

Smoking bans in psychiatric units

Public bans have reduced population smoking prevalence by de-normalising smoking and making it inconvenient to smoke.[46] Similar bans have been adopted in healthcare settings for more than 20 years in the USA and 10 years in Australia[47,48] but these bans have been slowly and inconsistently implemented in mental health facilities.[49,50] The high prevalence of heavy smoking among the patients and staff sympathy for patients who have been denied the opportunity to smoke have probably played a role.[51] (Table 2)

Smoking bans in psychiatric inpatient units in Australia[52] have attracted a number of criticisms. One is that bans in secure psychiatric units are "cruel and inhumane" because they deny the "right to smoke" to patients who are involuntarily detained.[53,54] These critics suggest that these patients should be allowed to smoke in designated smoking areas so as to protect non-smokers while allowing smokers with SMI the right to harm only themselves.[55,56] Those who defend smoking bans in mental health facilities argue that designated smoking areas convey the message that smoking is acceptable for persons with SMI.[57]

Critics of smoking bans have also blamed them for acts of violence against staff, often on the basis of very weak evidence.[58–60] These critics place greater weight on rare acts of violence to staff and patients than on the far larger harms that smoking causes to patients.

Smoking bans have also been criticised as paternalistic violations of individual freedom that deprive patients with SMI of "one of their few remaining pleasures".[54,55] This claim assumes that smokers with SMI do not want to or cannot quit smoking when almost as many want to quit as smokers without mental illnesses.[24] They simply find it more difficult to do so because they are not encouraged or adequately supported in quit attempts and they spend considerable periods of time being in a social environment which normalises and reinforces heavy smoking.[57] For people with SMI in long-term residential care, smoking bans may represent enforced smoking cessation because smoking is not permitted on the premises and patients cannot leave the facility to smoke. This situation raises more ethical concerns but smoking is one of many freedoms that people living in these circumstances lose.

Cigarette smoking is highly addictive and quitting can be extremely challenging for very heavy smokers with SMI. Smoking bans may give these patients a chance to quit in the most favourable setting, without an opportunity to smoke, and with good access to medications and psychological support from health care professionals to manage their withdrawal

symptoms.[51] These advantages may be partially offset if bans deter smoking patients from seeking treatment although it remains to be seen how commonly this occurs.[58]

Another concern is increased toxicity from anti-psychotic medications (for e.g. clozapine and olanzapine) if persons on these medications abruptly stop smoking. In such cases, treating psychiatrists should make appropriate adjustments in drug dosage, monitor the person while an in-patient and arrange for dosage review after discharge, if the person resumes smoking.[61,62]

Smoking bans alone will not produce long term abstinence.[63] A humane policy would provide patients with access to nicotine while in hospital e.g. by providing NRT, counselling and other pharmacotherapy on admission. Cessation support should also be provided at discharge, and on return to the community.[64] This approach has encouraged post discharge quit attempts in patients discharged from a smoke free psychiatric hospital.[65] Government policies which subsidise pharmacotherapies and harm reduction options for people with SMI may be needed to help maintain abstinence. Training hospital staff in quit smoking and relapse prevention methods and correcting their misapprehensions about the effects of smoking bans could increase compliance with smoke free policies and reduce patient distress.[49,66]

Tobacco harm reduction

The most effective way to eliminate tobacco-related harm is to abstain from using any tobacco or nicotine products. This has long been the central aim of tobacco control policy. But should smokers who are unable to quit, or who take longer to quit, be encouraged to try THR, that is, to obtain nicotine in ways that are much less harmful than smoking cigarettes e.g. by using smokeless tobacco or e-cigarettes?

Contemporary public health discourse about THR is highly polarized, especially in the case of e-cigarettes. Opponents argue that e-cigarettes will deter smokers from quitting, serve as a gateway to tobacco smoking in adolescents and renormalize smoking. These concerns may only be properly assessed after years of observational research on the ways in which these products are used by smokers and non-smokers and their impact on smoking rates.

Opponents of THR believe that these potential risks are sufficiently severe to warrant pre-emptive bans on the sale of e-cigarettes. They would only allow their use for cessation if they are shown to be safe and effective for cessation. This approach is likely to limit smokers' access to e-cigarettes produced by the tobacco and pharmaceutical industries, the commercial entities best able to meet the large regulatory costs. This is the current policy in Australia and Canada and a policy advocated elsewhere.

In countries that have banned e-cigarettes, it is important to examine how well e-cigarettes help heavily addicted smokers (such as those with SMI) to either quit all nicotine use, or to switch to using these as a safer long term alternative to cigarette smoking. There are very good reasons why heavy smokers with SMI should be a high priority group for assessing the value of THR approaches.[67] These are summarised below.

1. Some people with SMI may be deterred from quitting smoking because they believe that smoking alleviates their depression and attentional-cognitive deficits and reduces the adverse effects of antipsychotic drugs.[17,68,69] They may receive little support and encouragement from mental health personnel to quit because of unfounded fears about destabilising their mental condition.[25]
2. Switching to non-smoked nicotine products could reduce the dose of some antipsychotic medicines required, because the non-nicotine components of tobacco

smoke increase the metabolism of some antipsychotic drugs which means that smokers need higher drug doses to achieve optimum plasma levels.[70]

3. People with SMI are more often exposed to social environments that promote heavy smoking e.g. spending time with peers and family members who smoke tobacco. This makes abstinence difficult to maintain.[71]
4. Smokers with SMI, especially those with psychotic illnesses are often socio-economically disadvantaged and spend a large proportion of their meagre income on cigarettes. Access to low cost or subsidised harm reduction products would not only be beneficial for their health by quitting cigarettes but would make more of their limited income available for living expenses.
5. People with SMI may struggle to quit smoking successfully because of their heavy dependence on nicotine.[20] Previous failed quit attempts could reduce confidence in making future quit attempts.[72,73] This may be expose them to smoking for much longer than other smokers. THR options used as an interim step towards quitting may reduce tobacco-related harms sooner and encourage quitting.
6. THR for smokers with SMI, would satisfy important bioethical principles of beneficence (doing good), non-maleficence (protecting from harm), autonomy (respecting individual freedoms) and justice.[74] It may also reduce some of the ethical concerns about enforced cessation in smoke-free mental health facilities, if residents are permitted to use non-smoked nicotine products.

Potential tobacco harm reduction products

Among the THR products that could be recommended are NRT, low nitrosamine smokeless tobacco products (for example snus) and e-cigarettes. NRT substantially reduces smoking in smokers with SMI.[75] There is insufficient evidence to justify the routine use of other harm

reduction products but there is enough evidence to justify clinical trials. For example, one clinical trial found that e- cigarettes and nicotine patches were equally effective in achieving abstinence at 6 months and equally acceptable to smokers taking medications for mental illness. [76] Another found that e- cigarettes significantly reduced smoking in smokers with schizophrenia.[77] Other trials are underway to test the efficacy and acceptability of e-cigarettes for cessation in smokers with SMI.[78,79](See Table 3)

E-cigarettes are considerably less harmful than tobacco cigarettes and may be more acceptable than NRT for both smoking cessation and THR because of their sensory and behavioural similarities to cigarettes.[80–82] Switching to snus is associated with substantial population health gains in Sweden.[83] It has not been tested as a harm reduction option among smokers with SMI, but a clinical trial of snus among general population smokers did not find it better than high dose nicotine gum.[84] Sales bans on these products in many developed countries such as Australia, New Zealand and the European Union (apart from Sweden) make it more difficult to conduct trials of THR.[85]

There is a strong case for conducting pragmatic clinical trials of THR in smokers with serious mental illnesses. These should include trials of the use of e-cigarettes both for cessation from of all nicotine and as a long term alternative to smoking in those who are unable to stop using nicotine without relapsing to smoking. Conducting clinical trials among people with SMI can be challenging as their complex health and social needs can make recruitment, retention and monitoring more difficult than trials in general population samples.[86] However, the extra investment and effort required to develop the evidence base for THR options for this population is warranted given the urgent need to reduce smoking among people with SMI.

Conclusions

Smoking prevalence is very high among persons with SMI. The reasons are not wholly clear but the main contenders are self-medication, shared vulnerability due to environmental (e.g. social determinants of health) and/or genetic risk factors and a possible causal role for smoking. These are not necessarily mutually exclusive: smoking may have positive effects on some symptoms of SMI but at the cost of worsening other symptoms and increasing premature mortality and severe morbidity.

Smokers with SMI appear to be as interested in quitting as smokers without these illnesses but find it difficult to quit and remain abstinent. Often, smokers with psychotic illnesses such as schizophrenia experience social isolation and stigma. This requires innovative approaches to improve their access to cessation methods that are effective in smokers in the general population.[87] We need better evidence on whether these are as effective in persons with SMI. We also need more research on the effectiveness of delivering interventions via social media and smartphone apps and on long term relapse prevention in persons with SMI.[88]

Questions have been raised about the ethics and effectiveness of smoking bans in mental health care facilities. These bans are often incompletely enforced because staff do not support them and are concerned about denying smokers who are treated involuntarily the “right to smoke”. The provision of NRT and other cessation aids during periods of hospitalisation should be an ethical minimum for the humane care of smokers with SMI. It should be accompanied by better efforts to encourage cessation after discharge. Comorbid alcohol and other substance abuse should not be considered a contraindication for smoking cessation in persons with SMI.

A good case can be made for evaluating the role of e-cigarettes in smokers with SMI who try and fail to quit smoking. Thought may also be given to allowing their use in designated areas within hospitals that have banned cigarette smoking.

Search strategy and selection criteria

Relevant literature was identified by searching prominent medical literature databases such as PubMed, Embase and CINAHL up to 7th March 2016 using the search terms "severe mental illness", "mental disorder", "psychiatric", "Schizophrenia", "psychosis", "depression" and "bipolar disorder" alone and in combination with "smoking" , "tobacco", "smoking cessation" , "quit smoking", "harm reduction" , "tobacco harm reduction" , "smoking reduction" "electronic cigarette" , "e-cigarette", "vaporiser", "cannabis" , "snus", "smoking ban" and "smoke free". Papers were also identified from authors' personal collections and from references cited in the included articles. More emphasis was placed on recent publications. We generated the final reference list on the basis of the articles' relevance to this paper. Preference was given to RCTs and Metanalysis of trials of cessation and harm reduction aids; and prospective observational studies and meta-analyses of these studies on associations between cigarette smoking and serious mental illnesses and impact of smoking bans in psychiatric hospitals.

The site www.clinicaltrials.gov was searched using the search terms: Smoking AND ("mental illness" OR schizophrenia OR depression OR bipolar). Only those trials which had their trial completion date listed as on or after January 2015 have been included in this list (Table 2). Trials with unknown status were excluded.

Contributors

All authors were involved in critically reviewing the literature. WH conceptualized the design and RS prepared the initial draft of the paper. All authors were involved in the subsequent writing and editing of the manuscript.

Declaration of interests

We declare no competing interests.

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Table 1: Hypotheses for relationship between SMI and smoking

Hypothesis	Examples of Evidence for Hypothesis	Examples of Evidence against Hypothesis
Self-medication: People with SMI take up smoking to relieve their psychiatric symptoms	***Major Depression*** • Nicotine stimulates nicotinic acetylcholine receptors (nAChRs) in the brain which act on the acetylcholine, dopamine, norepinephrine, serotonin and opioids systems to enhance cognition and improve attention, memory, and mood.[89] • Monoamine oxidase inhibitors in cigarette smoke may have and antidepressant effect by inhibiting the breakdown of dopamine and serotonin.[90] • People with depression experience stronger withdrawal symptoms and negative affect on stopping smoking and smoking cessation can result in relapse to depression.[7,91] • Some antidepressants (bupropion and nortriptyline) are effective for smoking cessation.[92,93] ***Schizophrenia*** • Depressed mood is common in persons with schizophrenia; so any antidepressant effects of smoking are relevant to schizophrenia.[94] • Nicotine improves attention in people who experience deficits in filtering responses to sensory stimuli.[90] Nicotine improves this deficit by activation of α 7 cholinoreceptors ,releasing Gamma-Aminobutyric acid (GABA)and decreasing glutamate.[95] • Nicotine may improve other sensory gating deficits such as prepulse inhibition (PPI) deficit and mismatch negativity (MMN) potentially improving startle responses and memory processing.[95–97] • Smoking relieves neuroleptic medication side effects such as	***Major Depression*** • Evidence demonstrates longer term improvement in depression and anxiety symptoms after smoking cessation.[27] • Most antidepressant drugs do not assist smoking cessation.[33] ***Schizophrenia*** • Smoking often starts before symptoms of schizophrenia appear.[100] • Nicotine does not have antipsychotic properties and treatment with antipsychotics does not aid in smoking cessation.[101,102]

	parkinsonian symptoms and cognitive impairment.[98,99]	
Shared vulnerability: Smoking and severe mental illnesses coexist because of shared genetic/environmental risk factors and neurobiological aetiologies	***Major Depression*** • Twin studies suggest that the relationship between lifetime risks of smoking and major depression is solely due to shared genes that predispose to both conditions.[18] ***Schizophrenia*** • Genetic and environmentally based neuropathological abnormalities in the hippocampus and prefrontal cortex may increase vulnerability to the rewarding effects of addictive drugs and to experiencing psychotic symptoms.[103] • Genes such as CHRNA2, CHRNB2 ,CHRNA7 have been associated with regions that increase the risk of schizophrenia.[104] ***Bipolar disorder*** • Common genes (COMT, SLC6A3, and SLC6A4) and gene networks have been associated with both tobacco use disorder and bipolar disorder.[105] • Epidemiologic studies show that nicotine dependence and bipolar disorder predict each other's development.[106] • Shared environmental factors such as alcohol and illicit drug use and childhood adversity predict the development of both smoking and bipolar disorder.[107]	***Major Depression*** • Family study of smoking and major depression did not find an increased risk of smoking among relatives of person with depression.[108] ***Schizophrenia*** • Genes strongly associated with an increased risk of developing schizophrenia are not associated with nicotine dependence or number of cigarettes per day.[109]
Causal: Smoking causes SMI	***Major Depression*** • Epidemiological evidence indicates that cigarette smoking is associated with an increased risk of depression.[110,111] • A recent meta-analysis of 26 studies reported that smoking cessation is associated with reductions in depression and	***Major Depression*** • The likelihood of developing major depression in daily smokers is lower than in depressed individuals who start daily smoking (OR 1·9 vs OR 3·0). The

	anxiety symptoms.[27] • Cigarette smoking may cause lower serotonin function in the hippocampus which may result in depression.[112] ***Schizophrenia*** • Nicotine increases dopamine release in the brain's reward system.[113] This is consistent with the hypothesis that psychotic symptoms are the result of increased levels of striatal dopamine.[114] • A meta-analysis of epidemiological studies shows that smoking often precedes the onset of psychotic symptoms, persons with psychotic symptoms are heaver smokers than those without, and these associations persist after controlling for potential confounders.[115]	association may also be confounded by history of alcohol use.[116] • A Mendelian randomization metanalysis discounted a causal relationship as it did not find an association between a genetic marker for nicotine dependence (CHRNA5-*A3-B4* variant) and depression.[117] ***Schizophrenia*** • There are few prospective studies testing this hypothesis[115] and stronger longitudinal evidence and biological links are needed to establish a link between nicotine use and psychosis onset.[118] The association between smoking and psychosis may be confounded by association between tobacco smoking and cannabis use.[119] Cannabis use is associated with earlier onset of psychosis, has a dose response relationship with psychosis risk,[118] and can produce psychotic symptoms in persons with and without psychoses.[120] Only half of the prospective studies in the meta-analysis of tobacco use measured cannabis use.[115]

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Table 2: Pros and cons of Smoking Bans

Pros of smoking ban	**Cons of smoking bans**
Protection of patients from smoking related harms	Infringement of the "right to smoke" for involuntary patients and long term residents of psychiatric care facilities.
Opportunity to quit smoking under the care of professionals and with access to smoking cessation therapies.	Deterrent to seeking in-patient psychiatric treatment
Protection of non-smokers from second-hand smoke	Possibility of severe withdrawal symptoms mimicking exacerbation of mental illness
Improvement in mental health on stopping smoking	Some patients may leave the facility unaccompanied or discharge themselves early in order to smoke
Possible reduction in doses of some anti-psychotic medications e.g. clozapine	
Prevention of relapse in patients and staff who have quit smoking	

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Table 3: Interventional trials for smoking cessation in people with severe mental illness.

Title of the study	Trial registry number	Psychiatric condition	Interventions	Completion date	Status
Smoking Cessation for Depression and Anxiety Treatment	NCT02002858	Depression and anxiety	Nicotine Patch, Depression and Anxiety Smoking Cessation Treatment and Educational-Support Psychotherapy	May 2016	Recruiting
Decision Support for Smoking Cessation in Young Adults With Severe Mental Illness	NCT01779440	Severe mental illness	Varenicline and Placebo	December 2015	Active, not recruiting
Effects of Varenicline on Smoking Lapse in Smokers With and Without Schizophrenia	NCT01850953	Schizophrenia	Varenicline and Placebo	May 2015	Completed
Trial of Integrated Smoking Cessation, Exercise and Weight Management in Serious Mental Illness: TRIUMPH	NCT02424188	Serious mental illness	TRIIUMPH Intervention	June 2019	Not yet recruiting
Smoking Cessation for Depressed Smokers	NCT00494728	Major Depression	Smoking Cessation Treatment, Nicotine Replacement Therapy and Cognitive Behavioural Analysis System of Psychotherapy (CBASP)	December 2016	Active, not recruiting

Effects of rTMS on Cigarette Smoking and Cognition in Schizophrenia	NCT01523730	Schizophrenia	Repetitive Transcranial Magnetic Stimulation (rTMS) and Sham Repetitive Transcranial Stimulation (rTMS)	September 2015	completed
Behavioural Activation and Varenicline for Smoking Cessation in Depressed Smokers	NCT02378714	Depression	Varenicline; behavioural activation for smoking cessation (BASC) and Standard treatment	August 2020	Recruiting
Novel Smoking Cessation Drug for Schizophrenia	NCT02230384	Schizophrenia	A novel drug and a placebo	December 2016	Recruiting
Study Evaluating The Safety And Efficacy Of Varenicline and Bupropion For Smoking Cessation In Subjects With And Without A History Of Psychiatric Disorders(EAGLES)	NCT01456936	With and without psychiatric disorders	Placebo, varenicline, bupropion hydrochloride and Nicotine Replacement Therapy Patch	January 2015	Completed
Mobile Health Technology to Enhance Abstinence in Smokers With Schizophrenia	NCT02420015	Schizophrenia	Nicotine replacement therapy, Bupropion, cognitive-behavioural smoking cessation counselling, Mobile Contingency Management, Stay Quit Coach (smartphone application), SMS text messaging	March 2018	Not yet recruiting
Effects of Deep Breathing, Self-Help Book in	NCT02693561	Anxiety and depression	Deep Breathing Exercises and Self-Help Book	August 2016	Recruiting

Cigarette Consumption, Anxiety, Depression and Motivation to Stop Smoking					
Smoking Cessation Following Psychiatric Hospitalization	NCT02204956	Severe mental illness	Extended Care and Brief Education	June 2019	Not yet recruiting
Electronic Cigarettes in Smokers With Mental Illness	NCT02212041	Schizophrenia, Schizophreniform Disorder, Bipolar Disorder	Disposable electronic cigarette s	June 2016	Not yet recruiting
Telephone-based Smoking Cessation	NCT02500589	Depression	Behavioural mood management and Health education	June 2019	Not yet recruiting
Smoking Cessation And Reduction in Depression	NCT02124187	Depression	Ecig containing 24 mg nicotine, Ecig containing 0mg nicotine and Nicotine free inhalator	December 2017	Not yet recruiting
Acute Effects of Exercise in Smokers With Schizophrenia	NCT01635075	Schizophrenia	Exercise and passive control	January 2015	Completed
Transcranial Direct Current Stimulation (tDCS) As A Treatment For Cigarette Craving and Cognitive Deficits in Schizophrenic	NCT02128919	Schizophrenia	Device: tDCS	December 2017	Recruiting
Randomized Controlled Trial (RCT) of a Motivational Decision	NCT02086162	Schizophrenia	Web-based motivational decision support system; and NCI (national cancer	March 2017	Recruiting

Support System			institute) Education		
Vigorous Exercise for Depressed Smokers	NCT01860924	Depression	Exercise and health education	December 2015	Completed
Exercise for Depressed Smokers	NCT02086149	Depression	Aerobic Exercise and Health Education	September 2018	Recruiting
Nicotine Receptor Density & Response to Nicotine Patch: Pt 2 Extended Treatment	NCT02676375	Schizophrenia	Standard therapy of Nicotine patch or bupropion and extended treatment with combination drugs with and without home visits and phone calls.	February 2017	Active , not recruiting
Effects of Varenicline on Plasticity in Schizophrenia	NCT01934023	Schizophrenia	Varenicline and Placebo	August 2015	Completed
Efficacy of N-Acetyl-Cysteine in Bipolar Disorder and Tobacco Use Disorder	NCT02252341	Bipolar disorder	Dietary Supplement: N-Acetyl-Cysteine	September 2015	Enrolling by invitation
Very Low Nicotine Cigarettes in Smokers With Schizophrenia	NCT02019459	Schizophrenia	Very low nicotine content cigarettes and standard nicotine content cigarettes	August 2018	recruiting
Contingency Management, Quitting Smoking, and ADHD	NCT02266784	ADHD	Contingency Management (CM); Transdermal nicotine skin patches (i.e. Habitrol) and Supportive Counselling	October 2019	Recruiting
Behavioural Activation for Smoking Cessation in Veterans With PTSD	NCT01947725	PTSD	Nicotine patch, Nicotine gum or nicotine lozenge, Standard Smoking Cessation	September 2018	Recruiting

			Therapy, Health and Smoking Education, Behavioral Activation Treatment		
CPT and Smoking Cessation	NCT01901848	PTSD	Cognitive Processing Therapy (CPT), Bupropion, nicotine replacement therapy (NRT), Integrated Care for Smoking Cessation (ICSC), smokefreeVET program	April 2018	Recruiting
Integrated PTSD and Smoking Treatment	NCT01988935	PTSD	Prolonged Exposure and Smoking Cessation counselling	June 2018	Recruiting
Behavioural Activation for Smoking Cessation in PTSD	NCT01995123	PTSD	Behavioural Activation Therapy, Health and Smoking Education and Standard Smoking Cessation Therapy	December 2018	Recruiting
Improving Functional Outcomes of Veterans With PTSD and Tobacco Dependence	NCT02576899	PTSD	Acceptance and Commitment Therapy for PTSD and Tobacco Use; and Freedom From Smoking program	August 2017	Recruiting

Table 4: Pros and cons of using e-cigarettes for THR

Pros of electronic cigarettes	**Cons of electronic cigarettes**
A cleaner source of nicotine than cigarettes when use for self-medication	Limited research on the harms or benefits of their long term use
More economical than cigarettes in the long term	Initially an electronic cigarettes kit costs more than a pack of cigarettes.
Provides the socio-behavioural aspects of smoking on quitting.	Some electronic cigarettes might be difficult to use by people with severe mental illness
May result in smoking cessation/reduction because of diminished addiction potential of nicotine in the absence of any monoamine oxidase (MAO) inhibitors present in cigarette smoke.	